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THE IMPACT OF REGULATORY CONSTRAINTS ON FORMATION AND GROWTH OF BIOMEDICAL AND PHARMACEUTICAL START-UPS[1,2]

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Abstract

This paper applies the theories of technological innovation to the process of formation and growth of biomedical and pharmaceutical firms. It is based on detailed data gathered from 26 firms, founded between 1968 and 1975 in the Commonwealth of Massachusetts. These data were supplemented by a three-member expert panel evaluation of the risk associated with use of each firm's products.

A positive relationship was established between the level of technological sophistication of the firm and the risk associated with use of its products. Consequently, technological advancement of the firm has not necessarily resulted in high economic performance, in part because of the high demands put upon the firm's resources and time by the U.S. Food and Drug Administration approval process. Firms dealing with medical devices and pharmaceuticals were more sensitive to this regulatory process than those producing auxiliary products.

Enactment of the 1976 FDA regulations affecting medical devices was found to create a precarious environment for the marketing of new products. The impact of the amendment was found to be not limited only to its target product area, medical devices and supplies, but also challenged the management of firms producing drugs and pharmaceuticals.

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2 Our gratitude goes to Professor Stan Finkelstein of MIT, and to the entrepreneurs who shared their experience and insights with us.

Introduction: Studies of the Biomedical Industry

The estimated volume of the U.S. biomedical and the pharmaceutical industry is quite significant, approximately 25 billion dollars in 1980 (Gibson et al., 1983; Frost and Sullivan, 1983). Yet studies of the biomedical industry have focused principally on a few key issues. Coleman, Katz & Menzel (1966) studied the diffusion of medical innovations into adoption and use, finding it to be a two-stage communication process. The analysis of medical innovations by Bernstein, Beaven, Kimberly, and Moch (1975, 79-114) focused on diffusion-relevant attributes of medical technology. Recently Leonard-Barton (1983) used similar concepts to study the diffusion of periodontal techniques and materials.

Ashford, Butler and Zolt (1977), Young (1982), and Wardell (as cited in Roberts, 1981) analyzed the pharmaceutical industry and the influence of the Food and Drug Administration (FDA) on its productivity and innovativeness. Another direction followed by Fuchs (1974), Measday (1977), and Temin (1979) focused on the changes in the pharmaceutical industry, historically analyzing the interaction among technology, regulation and the economics of this industry.

A third research perspective is on the applicability to the biomedical industry of the theory of technological innovation. Comroe and Dripps (1977) rigorously analyzed the relation between basic research and its application in two areas of medicine. The Committee on Technology and Health Care of the National Academy of Science (1979) provided rich conceptual background for the analysis of equipment-embodied technologies but utilized little empirical data. Recently, Finkelstein and Homer (1984) applied simulation modeling to the issues of FDA policy decision-making in the face of the trade-off

between the public benefits from novel medical technologies, and the higher risks associated with their use. Roberts et al. (1981) synopsized much of the innovation research literature as interpreted in terms of the biomedical industry.

The biomedical industry is idiosyncratic on several counts (Moskowitz et al., 1981: 6-7). First, the industry is extensively regulated by the federal government, especially by the Food and Drug Administration. The extent of this external interference and control of quality standards is overwhelming, including both the efficacy and the safety of the product (pars. 510-515, FDA, 1976). The regulations also include directions about manufacturing and record-keeping procedures (par. 501), and labeling and advertising standards (par. 502). Both sets of standards are far more rigorous than standards which apply to nonbiomedical industries (FDA, 1976).

Second, the industry is supplying its products and technologies in a complex industrial goods market (Roberts, 1981), in which medical practitioners serve as intermediaries between producers and ultimate users - the patients. It should be noted that in this industry, relative to others, many practitioners have closer relationships with researchers because they have the opportunity to interact in their natural work environment - the hospital. This is especially true for those practitioners who are associated with academic medical center "teaching hospitals".

Third, the biomedical industry is an all encompassing name for a wide variety of products, embodying such scientific and engineering disciplines as biology, anatomy, microbiology, physiology, electronic and mechanical engineering, material and computer sciences, and many others. The various configurations of these disciplines present a

wide range of proximity to the clinical "core" of the industry. It is not clear what proportion of so-called biomedical firms produce diagnostic or therapeutic products of significance for the patient. How "medical" are these products, and to what extent are the idiosyncracies described above typical of them?

The conceptual model presented by Moskowitz et al. (1981, 3-5) sets a structured research agenda for the biomedical field. This model (Figure 1) consists of two distinct processes - the

Figure 1 approximately here

progression of technology from ideas to products and practices, and the interactions among people which facilitates this flow. As can be seen, these processes operate in a specific regulatory and marketing environment, which determines to great extent their structure, direction and intensity.

The small and comparatively young biomedical firm, founded by an entrepreneurial individual or group with the explicit objective of commercializing a product or technological knowhow, in addition to being interesting for the understanding of formation of new enterprises, also represents the junction of these processes. The small biomedical firm contains all the stages of biomedical innovation, from idea generation through to its communication, utilization and development, and up to its diffusion into practice. As a research locus the small firm should also contain sufficient data about most of the sources which influence innovations listed by Roberts (1981), such as staffing, idea generation and exploitation,

and structural and strategic issues.The perspectives which seem relevant both to the biomedical industry and to the specific setting of the small newly founded enterprise are those of: a)technology-based entrepreneurship and b)technology transfer.

Research Questions and Hypotheses

Technology, Risk Associated with Use, and the FDA

The central issue of the study described in this paper is the interaction between technology and risk associated with use (RAWU) of a firm's products, the influence of the FDA regulations on this interaction, and the resulting commercial performance of the firm. The studies of innovations in the pharmaceutical industry, e.g., Ashford et al. (1977), Young (1982), the Committee on Technology and Health Care (1979), and Bernstein et al. (1975), present strong evidence for the significance of the interplay between regulatory constraints and innovativeness in this industry.

Wardell (1974) points to the fact that extensive regulations in the United States decreased research productivity as measured by the number of new chemical entities (NCE) presented to the FDA for approval. He also showed (as cited in Young, 1982) that between 1962 and 1971 Britain led with respect to drugs available in both nations, calculated in terms of drug-years of prior availability. Britain also "..possessed nearly four times as many exclusively available drugs as did the United States" (Young, 1982, p. 19), mainly because the regulatory constraints there have not been as severe as in the United States.

Moreover, "This over-regulation had increased drug industry costs, driven a great deal of research overseas or into safer generic

areas, slowed or blocked the release of useful drugs"[our emphasis]. The amendment to the FDA Act in 1962 is described by Young (p.19) as "therapeutic disaster". Ashford et al. (1977) voice the same sentiments with some reservation related to the complexity of cost-benefit analysis of the impact of the FDA regulations.

Finkelstein and Homer (1984) show how sensitively a new medical technology's utilization can be influenced by government regulations. The simulated comparison between the regulated and the unregulated environment encountered by a new implantable heart pacemaker technology indicates that heavier regulations might delay a product's technical evolution by one and a half years, and somewhat inhibit its sales growth during as much as the first twelve (!) years after the new technology is introduced.

All these suggest that technological attributes of medical innovations are associated with the extent of FDA influence on their development. Important strategic implications for the biomedical firm also stem from the regulatory process, related to costs and schedules, product strategy, and possibly marketing strategy. A product's safety, or its inverse, the risk to patients and/or practitioners associated with its use (RAWU), is a strong determinant of the time delay and costs engendered by the federal approval process. Consequently, the financial requirements when founding a firm may become quite substantial in order to weather prolonged periods of commercial inactivity caused by the rigor of the FDA evaluation process for new products.

FDA regulations partition the product-areas of the biomedical industry into drugs and pharmaceuticals, medical devices, and para-medical products and supplies. The last two categories were

first regulated by Congressional action in 1976.

The research questions addressed in this paper stem directly from the studies of the pharmaceutical industry and of the technological innovation process, and the continuing gaps in the research pertaining to the biomedical industry: a) To what extent does the choice of product area, whether drugs and pharmaceuticals, medical devices, or products that are farther removed from the clinical core of the industry (dubbed by us as "auxiliary products"), influence the subsequent performance of the firm? b) What is the interaction between technological sophistication of a firm's products and the risk associated with their use? c) To what extent do FDA regulations impact technologically novel biomedical products and the firms that generate them?

The specific hypotheses addressing the interactions among technology, risk associated with use (RAWU), and the impact of the FDA regulatory activity are:

H1: Technologically sophisticated or novel biomedical products, especially those featuring first-of-a-kind or special specifications, create perceptions of high risk associated with their use.

H2: The impact of FDA regulations is more significant for technologically novel biomedical products.

FDA regulations appear to challenge significantly the management of biomedical firms. This leads to the question, "What strategic choices are exercised by the management of biomedical firms to limit the FDA interference with their operations?" We hypothesize that:

The management of firms which operate in more extensively regulated product areas:

H3 Have greater concerns with appropriate selection of product strategy, and

H4 Employ marketing strategies which attempt to decrease the sensitivity of the firm to FDA regulations.

Understanding the impact of new FDA regulations on specific product areas can significantly improve the evaluation of such initiatives in the future. The question that should be posed in this context is what was the impact on the biomedical industry of the most recent regulatory changes, the 1976 FDA amendment? Here we hypothesize that:

H5: The regulatory environment for medical devices became more restrictive after the introduction of the 1976 amendment, lowering commercial performance of those firms which introduced their first products after 1976.

Finally, we should bear in mind that young firms are sensitive to the FDA regulations to such an extent that these firms have serious problems in coping with governmental impact, especially in heavily regulated product areas. Consequently it seems logical to assume that:

H6: A firm's commercial performance is influenced by its product area: performance of young firms manufacturing drugs and pharmaceuticals is lower than of those producing either medical devices or auxiliary products.

Sample Selection and Data Collection

The sampling procedure used in this study differs to some extent from those used in prior studies of new firms (e.g., Roberts,

1968; Taylor, 1982; Utterback et al., 1983; Meyer and Roberts, 1984). Although our sample was clearly purposive, we attempted to make it as complete as possible.

Our assumption was that the data pertinent to our hypotheses would be available from firms with several specific attributes. First, the firms should be approximately one decade old, to allow sufficient time since incorporation so that their commercial performance is of a more stable pattern, after the initial start-up turmoil. On the other hand, to facilitate collection of first-hand data directly from the founders, the firms should not be older than 15-20 years, which age would increase the probability of founders' death or relocation, or of change of ownership since incorporation.

Second, the firms should have been formed for the purpose of doing business in the biomedical or the pharmaceutical industry, to present a more focused picture about young company operations in this specific area. Multi-product conglomerates clearly do not fit this requirement.

Third, to present as much as possible a comprehensive picture of the biomedical industry, the firms should be vertically integrated from R&D to marketing. Consequently, the firm should be an independent legal entity, not an R&D, manufacturing, or marketing arm of a larger corporation.

Adhering to the above criteria, the process of sample selection consisted of seven stages:

1. Corporations whose names suggested either a medical, pharmaceutical, biological, or a general technical context were selected from the 1970 to 1975 Massachusetts State House incorporation records. Those firms which either did not have the required vertical

integration, were previously incorporated outside of Massachusetts, or (despite their names) did not actually operate in the biomedical or the pharmaceutical industry were screened out on the basis of direct review of their original records of incorporation in the State House registry. This stage reduced the population from 506 to 106 firms.

2. To extent possible the founders of the remaining firms were located. It should be noted that firms that had been dissolved were not eliminated from the sample, though they were extremely difficult to trace. Inability to locate founders or firm resulted in over half of the drop-outs from the sample at this stage. Experience with prior studies of entrepreneurs suggests that most of these drop-out firms had never really been activated, despite incorporation.

3. A structured interview was tested with four firms chosen from the target population, the questionnaire modified from earlier work by Roberts and Wainer (1971), Taylor (1981), and Utterback et al. (1982). The main factors that were tested were the time required to complete the expanded questionnaire and the relevance and clarity of the new questions related to the medical context. Following initial testing the research instruments were finalized, consisting of a self-administered questionnaire that contained mainly well-structured and simple questions, and an interview questionnaire, containing unstructured or complicated issues which required real-time clarifications or explanations.

4. Efforts were undertaken to enlist the founders' agreements to participate. Among those who were not willing to participate at this stage the common explanation was "Don't want to talk". As much as the specific causes could be traced, they were usually "preoccupation with the current problems of the firm", or "the experience was too

painful to walk through it again for research purposes".

These obstacles produced difficulties in obtaining information about the comparative performance or the product area of the firms which dropped out of the sample at this stage. As far as we can tell attrition biases are not significant. It is possible that the attrition of firms which were dissolved, or encountered severe operational difficulties, was comparatively high. At least one firm was under FDA investigation and was advised not to participate in the study for legal reasons. Drugs and pharmaceuticals were represented among the "drop-outs" (about 4-5 firms), but the distinction between medical devices and auxiliary products, based on the limited data in the State House objectives of incorporation, was more difficult to make.

5. The self-administered questionnaire was mailed to 32 founders of biomedical firms (excluding the pilot study), resulting in another 7 drop-outs for various reasons. Some of the reasons that were mentioned: "I'm too busy with my clinical research in X University"; "The firm does not exist anymore"; "The questionnaire is too long"; "He does not have the time, and he doesn't want to talk" (secretary); "Although I'm willing to participate, I'm leaving for business negotiation to Europe till the end of March".

There are no specific patterns of sample attrition at this stage, although again our data about the comparative economic success of drop-outs is incomplete. Of the drop-outs at least one firm has approximately 400 employees, and another is a successful producer of heart pacemakers. Two firms were active in the product area of drugs and pharmaceuticals and at least two were in auxiliary products.

6. Field interviews with 25 founders were conducted usually in

their office. The founders of firms that were dissolved were interviewed at their homes or at the offices of their present employer.

Three additional firms were screened out of the sample, two of them due to confounded background or inadequate data and another because it had actually been incorporated in the early sixties.

For the analysis of entrepreneurial background and the initial period of founding the firm, 28 cases were used, while for the detailed causal analysis, 26 cases were included. One of the 26 cases lacked data about entrepreneurial background, early founding, and financing.

The final sample included three firms from the pre-test, for which the data were collected in a slightly different format. Two firms that were actually incorporated in 1968 and 1969 were included in the sample, as representative of the agglomerates of firms founded by the same founders between 1965 and 1975.

The bias introduced by the various non-respondents appears mainly to be under-representation of the firms which were either dissolved, acquired by large conglomerates, or relocated to other regions of the U.S. For instance one non-participating firm had been undergoing acquisition by a Texas corporation, another was under federal investigation by the FDA, two relocated to Florida and California, and two founders just recently died (see summary of sample attrition in Appendix A).

On the other hand, the firms included in the sample appear to be representative of the population of medical instruments firms as described by Dorfman (1982) and by Hekman (1980). As also can be seen from the above anecdotal information about the reasons for

self-elimination from the study, the firms that were excluded were of a broad range of sizes and of economic performances. (See Appendix B for sample attributes.) The breakdown by year of incorporation of the sample selection and the data collection stages is summarized in Table 1.

Table 1 approximately here

7. In addition to data about the risk associated with use of their products that was collected directly from the entrepreneurs, we decided, due to the importance of this variable for causal analysis, to independently assess product risk by use of external experts.

Indicators and Measures

Technological attributes of the firm

The various technological attributes of each firm's products were evaluated by the entrepreneurs on quasi-Likert* ordinal scales. The aggregate indices of technological sophistication of a firm's products were computed by summing up the scores on the scales of the importance of a)new technology or first of kind, b)special purpose or special specifications, and c)calibre of product or personnel as competitive advantages of a firm's products. The reliability of the additive indices based on the above three measures for each of the products of the firms was sufficiently high to justify their use as a measure of a single construct. (Cronbach's alpha between 0.53 and 0.57; for detailed data see references next page footnote.)

Another method of aggregation was used to derive the overall product specific technological index. Product specific scores on the above three scales, considered as indicative of technological sophistication or advancedness (alphas ranged between 0.50 and 0.60), were summed, becoming the index of overall technological sophistication of the firm which was found to be highly reliable (alpha=0.70).

Technological attributes of founders' background

The technological attributes of founders' professional background and experience were ordinally scaled on technological sophistication and relevance. Entrepreneurs who held predominantly R&D or research positions were encoded as "high" on technological sophistication of their professional background, and all the others were encoded as "low" (see Appendix C-1 for relevant examples).

Entrepreneurs whose previous employment was predominantly in universities or hospitals were encoded as "high" on relevance and technological sophistication of their industrial background, those with medical or pharmaceutical industrial experience were encoded as "moderate", and the rest as "low" (see Appendix C-2 for relevant examples).

Technological sophistication of the sources of technology

The sources of product technologies and ideas were ordinally

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* For detailed discussion see:
Miller, D. C. (1983). Handbook of research design and social measurement (4th edition). Longman, NY & London; Novick. M. R., & Lewis, C. (1967). Coefficient alpha and the reliability of composite measurements. Psychometrika, 32, 1-13.

scaled on technological sophistication and relevance. Product technologies which came predominantly from universities and hospitals were encoded as "high" on relevance and technological sophistication, those mostly from the public domain were encoded as "low", and the rest as "moderate" (see Appendix C-3 for relevant examples).

Product ideas predominantly from universities, inventions, or from research consultants were encoded as "high" on relevance and technological sophistication. Refinements of existing products or evolution from past work were usually encoded as "low", with the necessary correction for entrepreneur's professional and educational background, and the rest as "moderate" (see Appendix C-4 for relevant examples).

Assessment of risk associated with use (RAWU)

The use of a panel of experts has been recommended for assessment of risk associated with use of novel technologies (Fischhoff, Lichtenstein, Slovic, Derby, & Keeney, 1982). The size of the panel (three members) corresponds to the recommendations of Libby and Blashfield (1978) and Rohbaugh (1979), who showed that increasing the size of the panel beyond three members offer only incremental improvements in reliability.

Our panel comprised three MDs in the early stages of their professional careers, who, independently of each other, estimated the risk associated with use of each firm's products. The dimensions that were evaluated by the panel included risk to medical personnel and to patients associated with use of the products, the invasiveness of the products, and the proximity of the products to the clinical high impact area of the industry.

The panel supplied its assessment of the RAWU as scores on quasi-Likert ordinal scales. The raw scores of the panel were aggregated consecutively on three levels: a)for an additive scale of the three panel members, which yielded a Cronbach alpha of 0.91; b)for an additive scale of the scores on "Risk associated with use to the patient" and the "Invasiveness" for each product, which yielded Cronbach's alphas between 0.92 and 0.96; and c)for the overall risk associated with use index of the firm, derived by summing up the product specific indices, which yielded a Cronbach alpha of 0.98. Starting from the second level of aggregation of the raw scores RAWU the resulting indices were treated as interval variables. (See Appendix D for descriptive statistics of the RAWU.)

Measurement of economic success

The evaluation of economic success is an interesting issue; several studies in the past used quite simple indicators of commercial success of new firms. Meyer and Roberts (1984) argue that growth rate of sales alone is unreliable because it is biased towards young, fast growing firms. They proceeded by dividing the growth in sales by the age of the firm, using an aggregate of the last three years to smooth for annual fluctuations.

Taylor (1981, 15-16) used growth rates of sales as a measure of economic performance, although he partitioned his sample into "relatively successful" firms, "..if [they have] average sales growth that places [them] in the top half of the sample, and if [they have] been profitable in at least two of the past three years" (p. 15), and "relatively unsuccessful" if they have not. It should be noted, though, that Taylor's sample has a wide distribution of the start-up

year: from 1960 to 1981. This factor presents acute problems of control for his study, especially for causal analysis. The Meyer and Roberts sample spans only eight years of corporate birthdates (1968-1976), compared with six years span for most of the firms in the sample used in the present study.

The significance of firm's age as a determinant of its sales was tested and the results could not reject the null hypothesis of no difference. On the other hand, to smooth temporary fluctuations of sales, we used the average of the annual sales between 1980 and 1983 as the indicator of firm's commercial success. This index was highly correlated with the 1983 market value of the firm, as estimated by the entrepreneur (R=0.92), with the average number of firm's employees for the same four years (R=0.95), and with the growth in annual sales (R=0.95), validating its possible use as a single measure of firm's success.

The Sample

The sample of this study is probably more representative of the biomedical firms which existed in 1983, than of the firms which have been founded between 1970 and 1975. This assumption is based on the low number of firms that were dissolved in the final sample (see Table 2), which is much lower than the common death rate of new start-up companies. On the other hand, the number of medical instruments firms

Table 2 approximately here

that existed in Massachusetts in 1979 (Dorfman, 1982) was 105, similar to the number of firms that were still in the sample after the second selection stage.

The legal status of the firms in the sample is presented in Table 2. Additional descriptive information about the firms in the sample, including their business classification, and their product areas are provided in Appendix B.

Operating in a regulated environment: The interaction of technological innovation, risk associated with use, and the FDA regulations

Before we address the main issues of this section, dealing with the causal relations among technology, risk associated with product use, and the impact of FDA regulations, it is important to understand the various dimensions of the FDA requirements which bear upon the biomedical firm.

Sixty five percent of the products of the firms in our sample were regulated by the Bureau of Medical Devices of the FDA and 27% by either the Bureau of Drugs or Biologicals. Only two firms considered themselves not regulated at all, either because they had launched their products (medical devices or auxiliary products) before these categories were included in the FDA regulations, or because their products were quite removed from the clinical and consequently the regulated core of the industry.

The entrepreneurs reported that the FDA regulations influenced their product strategies on the average 3.2 points on a 5-point scale (64%), and their impact on the firm in general, as measured by the number of operational issues impacted by the regulations, 2.8 points on a similar 5-point scale (56%). Forty two percent reported that the

regulations were prone to inconsistent interpretations of the FDA examiners, and 19% claimed that their products had actually been misclassified by these examiners into wrong categories, probably due to insufficient FDA professional understanding.

The medical devices and auxiliary products in our sample were mostly of FDA classes I and II (86%), which require nonclinical proof of safety and efficacy, while 14% were of class III, requiring clinical tests. The former products were usually approved in the frame of paragraph 510K of the 1976 amendment, which is known in the industrial jargon as the "510K form". Those firms had to wait on the average between 45 and 90 days for "approval from Washington", though for most of the firms (62%) the process did not take more than 45 days. The approval process for class I and II products usually did not require more than one additional iteration, initiated usually by the FDA examiners due to some missing data, product misclassification or simply lost correspondence.

The climate for pharmaceutical and biological products is much more restrictive. Approval of an investigational new drug (IND) application for preliminary tests of efficacy takes between two and five years. The premarketing approval of a new drug application (NDA) has been of similar magnitude, resulting together with the IND in 6 to 10 years of iterative testing and application.

The sample firms' reported out-of-pocket expenses for external consultants, costs of clinical tests, special facilities or labeling procedures and other similar costs, range from none to $120,000 per annum, with a $30,000 median. We assume that neither figure includes lost revenues caused by the delays, nor the time spent by the founders.

At this stage it is interesting to know whether the above intervention by the federal authorities has been warranted by real issues of safety and efficacy of the products. Although our data do not address the cost-benefit analysis of government regulations, we tested whether products which were evaluated by the experts panel as having high RAWU drew more "fire" from the FDA . The data presented in Table 3 support the overall validity of at least the direction if not

Table 3 approximately here

the intensity of the FDA intervention. The correlations between RAWU and the impact of the FDA regulations on the firm are statistically significant. It seems logical that the impact of the first product's RAWU was the most significant: launching a product of high risk associated with its use can be a quite critical event for a young firm. On the other hand, the increasing correlations between the FDA precipitated expenses and the RAWU of products 2 and 3 is more difficult to explain. We hypothesize that most of the FDA expenses related to the first product were perceived by the interviewed entrepreneurs as founding expenses, while the expenses related to the second and third products were perceived as operational, and were reported as such.

As we already know, the FDA regulations are much more restrictive for drugs and pharmaceuticals than for medical devices and auxiliary products. To what extent is this efficacy and safety control effort warranted by the differences in RAWU, inherent to these product areas? The answer to this question is affirmative: the expert panel

rating of RAWU, typical of each product area shows (Table 4) that the FDA differential emphasis is well grounded.

Table 4 approximately here

After the above analysis, which can be regarded as validity tests for the criteria and decision-making process of the FDA, our next step was to address the interaction between technological innovation, RAWU, and the impact of the FDA. According to our findings, products with high RAWU were developed by technologically advanced firms that employed new or first-of-a-kind technology (Table 5). Merely embodying special specifications or special purpose orientation for a firm's products was less correlated with RAWU, and the relation with calibre of product or personnel is quite unstable and statistically insignificant.

Table 5 approximately here

These bring us to the next issue: as shown by numerous studies (e.g., Roberts, 1968 ; Taylor, 1981), the "spin-off" process effectively transfers technology from previous employers to the new firm. It seems reasonable to assume, especially in the face of the relation between RAWU and the firm's technology, that the background imdustries and positions of the founders might influence the RAWU of

their firm's products. The results summarized in Table 6 seem counter-intuitive: founders with more technologically sophisticated and

Table 6 approximately here

relevant background developed products of lower risk associated with use than their less technologically experienced counterparts. A possible explanation for these results is that entrepreneurs with industrial experience that was unrelated to either the biomedical or pharmaceutical industries were less aware of the importance of the RAWU factor, consequently launching products whose technological level did not justify their comparatively high RAWU.

At this stage we have succeeded in establishing the link between RAWU and the impact of the FDA regulations, and between RAWU and the technological dimensions of the firm. It is interesting to test to what extent RAWU and technology are the two sides of the same coin; whether one is the inverse of the other. The relations between the technological dimensions of the firm and the impact of the FDA regulations on the firm are appropriately supportive of this hypothesis: firms whose products actually embodied new technologies or were first-of-a-kind spent more than others on the FDA interface ($R=0.34, N=19, p \leq 0.08$). On the other hand, merely having "special specifications or special purpose", or advanced "calibre of product or personnel" did not draw more rigorous regulatory intervention from the FDA. The overall technological index of the firm, which is the average of these dimensions, reflected the intermediate outcome of being

positively correlated with the FDA expenses (R=0.20), albeit not statistically significant.

These interferences with an innovative firm's operations, in addition to what we already know about the delays precipitated by the FDA approval process, present significant obstacles for survival and success of the new biomedical and especially the pharmaceutical firm. What were the strategic and the operational measures applied by management to reduce the sensitivity of their firms to this interference?

We assumed that a natural response would be higher awareness of the salience of product strategy, and consequently, more careful planning in the face of a more regulated environment. As drugs and pharmaceuticals are presumably more regulated than medical devices and auxiliary products, we assumed that firms producing these products would report higher awareness or stronger impact of the FDA regulations on their product strategy.

The first indicator of managerial awareness of higher risk associated with developing regulated products was the strong association between estimated commercial risk of launching these products and the extent to which these product areas were regulated. Medical devices and drugs and pharmaceuticals were perceived as much riskier undertakings than auxiliary products (Kruskal-Wallis test's significance of $p \leq 0.04$). This relation was corroborated by the correlations between the RAWU and the estimated commercial risk of firm's products, which were statistically significant for the first product (Spearman R=0.45, N=26, $p \leq 0.01$) and for the firm, measured as an average of its products (R=0.36, N=26, $p \leq 0.05$). This correlation for the second and the third products is also positive (R=0.21 and R=0.22, respectively).

The data presented in Table 7 are congruent with the above results, though the relation between the impact of the FDA on product strategy and the product area of the firm is not strong enough to reject the null-hypothesis. Still Gamma=0.17, the contingency coefficient equals 0.42, and Spearman's correlation of the same data is statistically significant ($R=0.33, N=19, p \leq 0.05$), corroborating the previous results.

Table 7 approximately here

Partitioning of the ordinal categories above into "Low" versus "Moderate" and "High" impact of the FDA on firm's product strategy, and into "Drug and pharmaceuticals" versus the other products produced the results summarized in Table 8. Although, in this grouping the association between product strategy and product area of the firm is marginally statistically significant, it does support the general direction of the hypothesis.

Table 8 approximately here

Another way that a firm might deal with the FDA constraints is to decreas e its exposure to the end-users market, consequently, avoiding to some extent the FDA regulations concerning labeling and advertising. Manufacturing of an intermediate industrial product for

original equipment manufacturers (OEMs), or for dealers and wholesalers is a way to operationalize the above objectives.

The data about the sales methods used and their comparative contribution to firm's revenues, presented in Table 9, do not support the above assumption: first, most of the firms use direct sales, which

Table 9 approximately here

include visits and calls to potential customers. Second, the firms in more regulated product areas use direct methods even more extensively, though the difference is not significant. Although producers of auxiliary products report direct sales to be the main conributors to their revenues, the difference indicated by one-way analysis of variance is still only of marginal statistical significance.

It is quite clear that the issues of strategic response of the management of biomedical firms to the FDA challenge are very relevant for understanding technological innovation in this industry. Due to the size of the sample our data do not allow further analysis of these issues.

The impact of the 1976 FDA amendment on economic success

The potential impact of new regulations or modifications of existing ones is of sustained concern to policy makers and evaluators of health care products. The products in our sample were launched between 1970 and 1983 (see Table 10 for details). The October 1976 amendment to the FDA regulation for the first time explicitly included

medical devices and other products and supplies. This created a

Table 10 approximately here

special opportunity to test its impact in a quasi-experimental setting, though still with only cross-sectional data. We assumed that the new regulations concerning medical devices and their implementation had significant effect on products introduced into the market after 1976. Second, the reported misclassifications, and arbitrary interpretations of the FDA regulations by the FDA examiners, were probably most intense during the transitory period of 1976-1977, creating a more precarious climate for new products. Third, not only had the recently regulated products been affected by the regulatory changes; at least in two cases, ophthalmological substances (one biological, one synthetic) were initially misclassified as devices, precipitating significant delays in company operations until the right category was found.

To address these issues we partitioned the sample in several ways. First, we compared the performance of the firms in the sample which launched their first products before 1976 with those who launched them from 1976 and later, with and without those firms whose products were not the target of the new regulations. From the data in Table 11 it is quite clear that the impact of the FDA had been very

Table 11 approximately here

significant, especially on mobilized resources, and on the scale of operations as represented by the number of employees.

An alternative explanation for the above relations might be the different age of the firms, with older firms launching their products before the younger firms in the sample, concomitantly having more time span for growth and stabilization. This explanation does not hold in the face of the fact that there is no correlation between the age of the firm and the year of launching its first product. In addition, to control for this possibility, and also to reflect the specificity of the transitory period of 1976-77, we divided the sample into three periods: before 1976, 1976-1977, and after 1977.

The results in Table 12 are inconclusive: the financial inputs for the firms which launched their first products in the transitory period are significantly lower than for other firms, but their sales between 1980-1983 are quite high in comparison. Consequently, although the anecdotal evidence provided by the entrepreneurs suggests that the transitory period had had a strong negative influence on their operations the quantitative data do not support it. It should be noted though that three out of four firms that were dissolved before 1983 launched their first products during this period.

Table 12 approximately here

It is interesting to note that the data of the whole sample emphasized the impact of the 1976 amendment on firms whose products had not been its direct target. Those firms still have been affected

by the regulatory turmoil and the general industrial climate. When the performance outliers are excluded from the sample the above differences are still statistically significant for the financial inputs and the number of employees at founding and between 1980-1983.

Summary

To summarize, it should be emphasized that although the data have not always supported the specific hypotheses with statistical significance, they reliably elicited the role of the FDA regulations as a significant constraint for young firms in the biomedical industry. The implications for technological innovation in this industry are quite unique: the more advanced are the products of the firm, the higher is the risk associated with their use, and consequently, the more articulated is the impact of the FDA regulations on a young firm's strategy, and performance. In the more regulated product areas, such as drugs or medical devices, the economic performance of the firm is significantly more impacted by the FDA. Finally, the impact of the FDA regulations was corroborated by the quasi-experimental setting of the 1976 amendment, which also succeeded in reflecting the impact of regulatory change on the target as well as on other related product areas.

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Figure 1: The biomedical research spectrum (Roberts et al., 1981: 7)

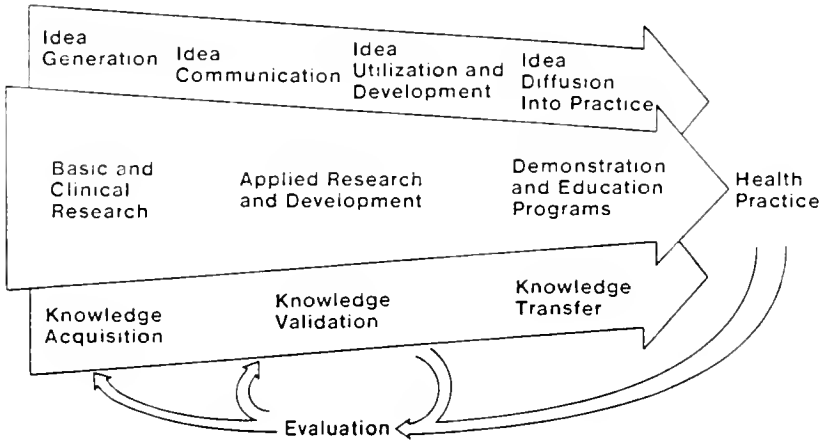

Table 1: Attrition of the initial sample during selection and data collection

Year of incorporation	Total	1970	1971	1972	1973	1974	1975
Initial sample	506	65	76	66	92	78	129
Stage 2 selection	106	13	19	20	13	9	32
Mailing list of questionnaires	36	5	5	7	4	6	9
Complete data collected	29	5	5	7	2	5	5

Note: A 1974 incorporated firm had actually been founded in 1968, and a 1975 incorporation had been stated in 1969.

Table 2: The legal status of the firms in the sample

Legal status of the firm	Frequency	
	Number	%
Independent	17	65
Dissolved	4	15
Being acquired	3	12
Owned by another firm	2	8
Total	26	100

Table 3: Impact of the FDA regulations and the risk associated with use of firm's products

Risk associated with use of firm's products	Overall impact[1] of FDA regulations N	R	Expenses for the[2] FDA interface N	R
First product	26	0.35**	19	0.20
Second product	19	0.29	15	0.32
Third product	16	0.14	13	0.51**
The firm (products average)	26	0.32*	19	0.47**

[1]Spearman and [2]Pearson correlations: *$p \leq 0.1$;**$p \leq 0.05$. Seven entrepreneurs could not evaluate their FDA interface expenses.

Table 4: RAWU typical of the product area

Risk associated with use of firm's products	Product Area: Auxiliary products	Medical devices	Drugs and pharmaceuticals	p of stat. signif.
N	6	14	6	
First product	22	11	12	0.005
Second product	15	8	8	0.05
Third product	14	7	7	0.1
The firm (products mean)	22	11	11	0.005

The table figures are mean rank sums. Higher sums indicate product with lower RAWU.

Table 5: RAWU and the technological dimensions of the firm

Technological dimensions of the firm	Risk associated with use of: First product	Second product	Third product
N	26	20	16
New technology or first-of-kind	0.34**	0.45**	0.33*
Special specifications or special purpose	0.06	0.09	0.06
Calibre of product or personnel	-0.14	0.10	-0.18

Pearson correlations: *$p \leq 0.10$; **$p \leq 0.05$. Positive correlations indicate association of high RAWU and high score on the technological dimensions.

Table 6: Professional background of the founders and the RAWU of firm's products

RAWU of the	N	Technological sophistication and relevance of Industrial background: Low	Moderate	High	p	Positional background: Not R&D	R&D	p
First product	23	13	9	16	NS	9	14	0.04
Second product	16	8	7	15	0.10	7	10	0.08
Third product	13	7	6	13	NS	6	8	NS
The firm	23	12	10	16	NS	9	14	0.10

The table figures are mean ranks sums. High mean rank sums indicate products with lower RAWU.

Table 7: Impact of FDA regulations on product strategy of the firm by product area

Impact of FDA regulations	Product area: Auxiliary products %	(N)	Medical devices with aux. prods. %	(N)	Drugs or pharma. with others %	(N)
Low	33	(2)	43	(6)	0	(0)
Moderate	0	(0)	21	(3)	33	(2)
High	67	(4)	36	(5)	67	(4)
Total	100	(6)	100	(14)	100	(6)

Table 8: Impact of FDA regulations on product strategy of the firm by product area (different grouping)

Impact of FDA regulations	Product area: Medical devices and auxiliary products %	(N)	Drugs or pharmaceuticals with others %	(N)
Low	40	(8)	0	(0)
Moderate or High	60	(12)	100	(6)
Total	100	(20)	100	(6)

Fisher exact test $p \leq 0.081$.

Table 9: Use of indirect sales and their contribution to firm's revenues by product area

Sales methods	Frequency of use — Product area: Auxiliary %	(N)	Devices %	(N)	Drugs %	(N)	Contribution to revenues — Product area: Auxiliary %	(N)	Devices %	(N)	Drugs %	(N)
Indirect sales	60	(6)	64	(14)	44	(4)	25	(1)	37	(3)	33	(1)
Direct sales	40	(4)	36	(8)	56	(5)	75	(3)	63	(5)	67	(2)
Total	100	(10)	100	(22)	100	(9)	100	(4)	100	(8)	100	(3)

Note: The distribution above is of those who answered the relevant questions. Up to two sales methods could be reported by each firm.

Table 10: Schedule of launching new products by biomedical firms in the sample

Year of market entry	First product %	N	Second product %	N	Third product %	N	Total products %	N
1970-1974	68	17	40	8	25	4	47	29
1975-1979	20	6	30	6	19	3	24	15
1980-1983	12	3	30	6	56	9	29	18
Total	100	26	100	20	100	16	100	62

Table 11: Financial and performance indicators and the 1976 FDA amendment

Financial and performance indicators	The whole sample: 1st product launched before '76	The whole sample: 1st product launched after '76	Excluding drugs and pharma.: 1st product launched before '76	Excluding drugs and pharma.: 1st product launched after '76
N	19	7	16	4
Equity (000)	102	11*	119	16*
Long-term financing (000)	1171	469	1369	40**
Average sales 1980-83 (000)	2621	1102	3047	1817
Average number of employees first two years	7	2**	8	3*
Average number of employees 1980-1983	54	8*	62	13*

T-test of means with separate variances: *p≤0.10; **p≤0.05.

Table 12: Financial and performance indicators and the 1976 FDA amendment; the transitory period of 1976-77

Financial and performance indicators	The whole sample: 1st product launched -76	76-77	77+	Excluding drugs and pharma.: 1st product launched -76	76-77	77+
N	19	3	4	16	2	2
Equity (000)	102*	18	6	120**	25	7
Long-term financing (000)	1171**	93	751	1367**	80	0
Average sales 1980-83 (000)	2622*	1977	446	3047*	2763	871
Average number of employees first two years	7	3**	1	8**	4	2
Average number of employees 1980-1983	54*	13**	4	62*	18	7

T-test of means with separate variances: *p≤0.10; **p≤0.05; the t-test was performed on each pair of means, with its significance specified on the connecting lines. It should be noted here that this procedure of multiple-comparison of means significantly increases the probability of Type I error. The new Type I error=$1-(1-p)^2$.

Appendix A: Sample attrition statistics (after stage 2)

Cause for Attrition	Total N	Year of Incorporation 1970	1971	1972	1973	1974	1975
Total set after selection for stage 2	106	13	19	20	13	9	32
1. Dental clinic	2						2
2. Not medical	2				2		
3. Only marketing	3				1		2
4. Actually incorporated too early	5	2	2	1			
5. Not originally incorporated in Massachusetts	1						1
6. Do not want to talk	16	2	3	2	2	1	6
7. No address or contact	47	4	9	10	6	3	15
8. Founder dead	2			1			1
9. Inadequate data	2	1	1				
Total attrition	80	9	15	14	11	4	27
The final sample	26	4	4	6	2	5	5

Appendix B: Sample descriptive data

B-1: Business classification

Business Definition	Frequency 1968-1975 N	%	1980-1983 N	%
Marketing only	2	8	-	-
Manufacturing only	3	12	3	12
R&D and consulting	4	15	-	-
R&D and manufacturing	6	23	6	23
From R&D to marketing	11	42	17	65
Total	26	100	26	100

B-2: Product area

Product Area	Frequency N	%	N	%
Auxiliary products	6	23	6	23
Medical devices	10	38		
Medical devices and auxiliary products	4	15	14	53
Drugs/pharmaceuticals	3	12		
Drugs/pharmaceuticals and auxiliary products	2	8		
Drugs/pharmaceuticals and medical devices	1	4	6	24
Total	26	100	26	100

Appendix C: Criteria and examples for encoding ordinal data

C-1: Type of work, job, position

Encode as "R&D" if work, position, or job was predominantly R&D or research. Encode "Other" for other.

Examples of job histories (the first position on the list is the most recent job):

1. Quality assurance, quality assurance, R&D - encode "Other".
2. R&D, self-employed - encode "R&D".
3. R&D, management, self-employed - encode "R&D".
4. R&D, marketing - encode "R&D".

C-2: Type of industry

Encode as "High" relevance and sophistication if predominantly university or hospital. Encode "Moderate" if predominantly medical or pharmaceutical industry. Encode "Low" for other.

Examples(as above):

1.Medical/pharmaceutical industry, and three previous jobs in high-tech industry - encode "Moderate".
2. Three recent jobs in high-tech, previous job in medical/pharmaceutical industry - encode "Low".
3. Chemical industry, university, medical/pharmaceutical industry - encode "Moderate".
4. Hospital, two jobs in high-tech industry - encode "High".

C-3: Sources of product technology

Encode "High" if sources predominantly university, hospitals. Encode "Low" if public domain. Encode "Moderate" if other.

Examples:

1. Government, university/hospital, license - encode "High".
2. Personal experience, public domain - encode "Low".
3. Purchased product line, public domain - encode "Moderate".
4. Personal experience, patent ownership - encode "Moderate".

C-4: Sources of product ideas

(see above - C-3)

C-5: Complementarity of founders' skills

Encode "High" with at least three co-founders with different skills. Encode "Moderate" with at least two different skills. Encode "Low" with either business or technical skills.

Examples:

1. Arts, Sales, MBA, Engineer - encode "High".
2. MBA, Engineer - encode "Moderate".
3. MBA, Sales - encode "Low".
4. Natural Science, MBA - encode "Moderate".

Note: Subsequently was recoded only into two categories of "High" and "Low" complementarity. The former included the original "High" and "Moderate" categories.

Appendix D: Descriptive statistics of RAWU

D-1: Distribution statistics of RAWU raw scores

	First Product		Second Product		Third Product	
N	26		20		16	
Statistics	PAT(*)	INV(*)	PAT	INV	PAT	INV
Mean	13.4	14.7	12.8	14.2	14.7	15.1
Median	13.8	16.0	10.5	16.0	14.5	18.0
Std. Dev.	5.5	5.9	6.2	6.4	5.6	6.6
Skewness	-0.3	-0.6	0.1	-0.4	-0.6	-0.8

* PAT = RAWU to the patient; INV = Invasiveness.

D-2: Distribution statistics of RAWU by products, and firm's average

	First Product	Second Product	Third Product	Firm
Statistics	N 26	20	16	20
Mean	28.2	27.0	29.8	27.9
Median	28.5	28.5	32.5	28.1
Std. Dev.	11.0	12.3	12.1	10.1
Skewness	-0.5	-0.2	-0.7	-0.4

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